Grayanotoxin Poisoning in Humans from Honey Consumption

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Objectives

The main objective of this bibliographic research is compiling and announcing information about grayanotoxin-containing honey and the toxic effects derived from its ingestion. This substance is believed to have medicinal properties, and the current increment of use of natural products as dietetic complements with this finality may cause a rising in the number of intoxication cases. So it is important learning to recognise the clinical signs it causes and their treatment, apart from finding out if it may have medicinal applications.

Introduction

The poisoning caused by grayanotoxin-containing honey, called “mad honey”, is known from antiquity. This toxic honey has been used for different purposes, such as biological weapon or therapeutical product.
The origin of this toxin relays in some plants of the *Rhododendron* genus, widespread all around the northern hemispheric. The most common species is *R. ponticum*, popularly known as “common rhododendron”, which contains high levels of grayanotoxins.
Grayanotoxins are non-volatile diterpenes, water- and lipid-soluble. There are 25 known isoforms, although the most toxic and abundant types are GTX-I and GTX-III, followed by GTX-II.
The ingestion of grayanotoxins causes mainly neurological and cardiac symptomatology in humans, even though they are not lethal at normal doses. The needed dose for the apparition of symptoms is [5, 30] g of honey. The clinical signs begin around [1.5, 3] hours after ingestion, and they disappear at most after 24 hours with a proper treatment.
The most common and outstanding signs of this intoxication include dizziness, weakness, hypotension, and bradycardia. In serious cases, important cardiac alterations may happen, such as AV block and arrhythmia.

Mad Honey in History

Mad honey poisoning was first described in 401 BC by Xenophon, who detailed its effects on soldiers subjected to the poisoning. A similar incident occurred in 97 BC, when King Mithridates Eupator of Pontus used it to defeat the Roman forces.
In his “Historia Naturalis”, Pliny the Elder identified the possible origin of this toxic honey in some plants of the *Rhododendron* genus. Dioscorides, Diodorus of Sicily, and Aristotle also refer to the effects of this poisoning.
Barton was the first American to report the effects of mad honey poisoning, in 1794. Additionally, in 1891 Plugge and Zaayer discovered that the active substance of several plants of the Ericaceae family, and of this honey, was andromedotoxin, currently known as grayanotoxin or GTX.

Plants Containing GTX

Grayanotoxins are found in some species of the *Rhododendron* genus, which comprises [800, 850] species. The most common is *R. ponticum*. Other species and families containing this toxins can be found on the table below.
To obtain this toxic honey, a great concentration of these plants is needed in a specific area. The main zone that meets this characteristics is the north-eastern part of Turkey, as seen on figure 1, where most of the mad honey cases are found.

Figure 1. Approximated distribution of *R. ponticum* in Turkey.

Species	Family	GTX[a]
Agauria spp.	Ericaceae	+
Andromeda spp.	Ericaceae	
Pieris japonica	Ericaceae	+++
P. floribunda	Ericaceae	+++
P. formosa	Ericaceae	+++
Rhododendron sp.	Ericaceae	
R. luteum	Ericaceae	++
R. ponticum	Ericaceae	++
R. occidentale	Ericaceae	+
R. macrophyllum	Ericaceae	+
R. albiflorum	Ericaceae	+
R. maximum	Ericaceae	++
R. japonicum	Ericaceae	+
R. catawbiense	Ericaceae	+++
R. decorum	Ericaceae	++
R. mucronulatum	Ericaceae	++
Kalmia sp.	Ericaceae	
K. latifolia	Ericaceae	+
K. angustifolia	Ericaceae	+++
K. polifolia	Ericaceae	+++
Pernettya sp.	Ericaceae	
P. coriaceae	Ericaceae	++

[a] Possible presence level (spectroscopic and chromatografic data): + less; ++ mid; +++ high.

Structure, Types and Isolation of GTX

Grayanotoxins are non-volatile diterpenes, a polyhidroxylated cyclic hydrocarbon with a 5/7/6/5 ring structure that does not contain nitrogen, as seen on figure 2. There are 25 known isoforms of grayanotoxins, GTX-I and GTX-III being the most common and abundant ones, followed by GTX-II.
The GTX can be isolated by typical extraction procedures for naturally occurring terpenes, such as paper electrophoresis, thin-layer chromatography (TLC), and gas chromatography (GC). They require derivatization before GC analysis due to the compound’s instability on heating and having low vapor pressure. Other identification techniques are based on infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS).

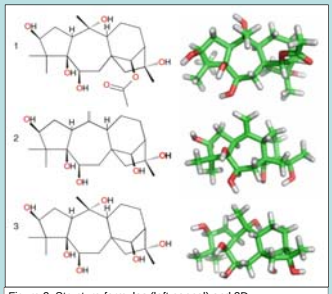

Figure 2. Structure formulas (left pannel) and 3D representations (right pannel) of GTX-I, II and III.

Mechanism of action of GTX

The toxicity of GTX relays on their capacity to bind to Na+ channels in their open state, so they lose the inactivation process and their activation voltage shifts to the direction of hyperpolarization. This causes a persistent activation of the Na+ channel. The site of union of the GTX is most probably located on the inner side of the membrane.
This action translates to marked bradycardia and respiratory depression. Peripheral vagal stimulation appears to play a role in grayanotoxin-induced bradycardia, since there is no bradycardia on bilaterally vagotomized rats. Also, muscarinic M2-receptor subtypes are involved in the cardiotoxicity of GTX, but not in respiratory toxicity, since those receptors mediate vagal stimulation on the myocardium.
GTX stimulates the parasympathetic nervous system and induces a rising of insulin secretion on the pancreas, decreasing blood sugar in diabetic rats, although it also causes toxic effects on a renal and hepatic level. None of these alterations has been found on humans.

Clinical Signs and Treatment

Mad honey poisoning causes mainly neurologic and cardiac symptomatology, though it is rarely fatal for humans. The dose needed for the apparition of signs is [5, 30] g of honey, and the effects can be first seen [1.5, 3] hours after ingestion. The signs disappear after 24 hours.
The most common signs are summarised on figure 3. Serious intoxication may lead to important cardiac changes, such as AV block and arrhythmia.
The clinical manifestations are similar to those of a cholinergic toxidrome, even though pseudocholinesterase levels are not decreased in poisoned patients.
Intravenous atropine, normal saline infusion, and usual supportive care with electrocardiographic monitoring should be treatment enough in most cases. If not, Advanced Cardiac Life Support bradyarrhythmia protocols or a temporary transvenous pacemaker should be considered.

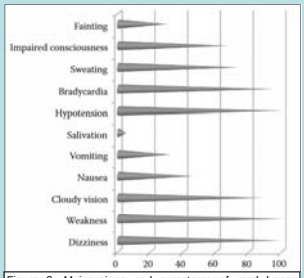

Figure 3. Major signs and symptoms of mad honey poisoning (%).

Medical Applications

Plants containing grayanotoxins, as well as toxic honey, are traditionally used in some places to benefit numerous ailments, such as gastrointestinal alterations, common cold, arthritis, hypertension, rheumatism, and fungal skin infections. They are also used as analgesic and sexual stimulant.
Although research on the medicinal use of these products has revealed initial results confirming some of those traditional beliefs to some extent, further studies are needed. Their hypotensive and bradycardic effects could be useful in the treatment of cardiovascular diseases.

Conclusions

In a patient suspected of having GTX poisoning, a complete clinical examination is needed. Finding out if toxic honey or other grayanotoxin-containing products have been ingested in the last hours is vital, and a sample of the suspected substance should be saved for later identification of the toxin. Also, treatment should be initiated as soon as possible.
So far, the medical properties of GTX have not been studied, that is the reason why the use of grayanotoxin-containing products in complementary medicine should be avoided.
Honey produced on the eastern area of the Black Sea, in Turkey, should be carefully consumed in order to avoid mad honey poisoning. The risk of poisoning by grayanotoxin-containing honey is lower in other parts of the world and in industrially produced honey, since the concentration of toxins is extremely low and honey of diverse origins is mixed up during the procedure.
Lastly, further study on the GTX hypoglycemiant properties in animals should be conducted. It should be determined whether if this effect appears also in humans, since it could be useful in the treatment of diabetes mellitus.

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